

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Roger R. C. New

Serial No.: 10/553,169

Filed: April 15, 2004

For: UPTAKE OF MACROMOLECULES

DECLARATION

I, Roger R. C. New, do hereby declare and state as follows:

I am the inventor for US Serial No. 10/553,169 and have a thorough knowledge of the invention.

In the Office Action that issued on this application with a mail date of 5 August 2008 the Examiner suggests that it would have been obvious to add propyl gallate (PG) or butyl hydroxyl anisole (BHA) to a composition as described in the prior art document US 5,853,748. The compositions described in US 5,853,748 contain, *inter alia*, a bile acid or salt together with an agent with the ability to adjust the pH in the gut to a value of from 7.5 to 9. A preferred bile acid used in US 5,853,748 is chenodeoxycholate. A preferred pH adjuster used in US 5,853,748 is sodium bicarbonate.

I have conducted experiments to investigate the stability of an aqueous solution containing, along with chenodeoxycholate, sodium bicarbonate at low pH after the addition of a small quantity of acidity regulator.

A solution in water was prepared containing 100mg of chenodeoxycholic acid sodium salt, and 50mg of sodium bicarbonate in a total volume of 4ml. 1ml of this solution (containing 12.5mg bicarbonate) was transferred into a measuring tube, and the pH determined using a calibrated pH meter. The initial pH was found to be between 8.35 and 8.37. In the first experiment, sequential additions of 20ul of 0.1N HCl were added, with vigorous mixing and measurement of the pH between each

addition. A total of 1.1ml of HCl was required to bring the pH down by approximately 1.5 units, whereupon the solution precipitated at pH 6.70.

In a second experiment, a solution of a standard pharmaceutical acidity regulator, citric acid, was prepared at a concentration of 35mg/ml (175mg in 5ml distilled water – 0.5N). 20ul aliquots of this solution were added to a second sample of chenodeoxycholate/ bicarbonate, with mixing and pH determination being carried out between each addition. Once again, precipitation occurred close to pH 6.7. The total amount of citric acid added before precipitation was 320ul, containing 11.2mg of citric acid, and 8.4mg of citric acid was required to bring the pH to neutrality.

This weight of citric acid is close to the weight of the bicarbonate in the original sample, indicating that, because the buffering capacity of bicarbonate is so high, in order to bring the pH of the formulation in '748 down to a level below 7.0, an amount similar to the amount of bicarbonate itself would need to be added, which is inconsistent with the idea of using the acidity regulator as a fine-tuning agent.

More importantly, the experiments demonstrate that neither the presence of bicarbonate, nor citric acid, permit the chenodeoxycholate to be soluble at pHs found in the small intestine (about pH 6.5 if fasted, about pH 5.5 if fed), since precipitation was noted in both cases at approximately 6.7.

Thus, one skilled in the art, with knowledge of '748, and using the methods described above to lower the pH, would not be motivated to continue experimentation starting from a formulation based on '748.

I acknowledge that willful false statements and the like are punishable by fine or imprisonment, or both, and may jeopardize the validity of the application or any patent issuing thereon. All statements made of my own knowledge are true and all statements made on information and belief are believed to be true.

Signed

This 31<sup>st</sup> Day of July 2009.